

**Mipomersen (KYNAMRO®)****National Drug Monograph****May 2015****VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

**FDA Approval Information<sup>1</sup>****Description/Mechanism of Action**

Mipomersen (KYNAMRO®) is the first-in-class antisense oligonucleotide (ASO) inhibitor directed at inhibiting the production of human apolipoprotein B-100 (ApoB). Apolipoprotein B is the major structural lipoprotein of very low-density lipoprotein cholesterol (VLDL-C). Reduced availability of ApoB results in reduced production of VLDL in the liver and therefore less VLDL is released into the circulation. Reduced VLDL results in lower levels of low-density lipoprotein cholesterol (LDL-C) and other lipoproteins. Additionally, VLDL transports triglycerides (TGs) from the liver into the circulation. Therefore, lower levels of VLDL results in accumulation of TGs in the liver.

**Indication(s) Under Review in this document (may include off label)**

Mipomersen is approved as an adjunct to lipid-lowering medications and diet to reduce LDL-C, ApoB, total cholesterol (TC) and non-high density lipoprotein cholesterol (HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

- The safety and effectiveness of mipomersen has not been established in patients with hypercholesterolemia who do not have HoFH.
- The safety and effectiveness of mipomersen as an adjunct to LDL apheresis is unknown; and therefore the treatment combination is not recommended.
- The effect of mipomersen on cardiovascular morbidity or mortality is unknown.

**Dosage Form(s) Under Review**

The dose of mipomersen is 200 mg given subcutaneously once a week on the same day.

**REMS**

☒ REMS ☐ No REMS ☒ Post-marketing Requirements  
See Other Considerations for additional REMS information

**Pregnancy Rating**

Category B. Use in pregnancy only if clearly indicated.

**Executive Summary****Efficacy**

- The FDA approval of mipomersen was based upon one phase III clinical trial conducted in patients with HoFH and three phase III trials conducted in patients at high risk for cardiovascular disease but without a diagnosis of HoFH (refer to the off-label section for a summary of trials in patients without a diagnosis of HoFH). A total of 390 patients were included in these trials and were randomized 2:1, mipomersen to placebo.
- In the trials of patients on maximum statin doses, LDL-C was reduced 24-28% in patients with HoFH on statins +/- other lipid-lowering drugs; 21-37% in patients with severe hypercholesterolemia on statins +/- other lipid-lowering drugs; and up to 47% in patients with statin intolerance vs. placebo. Other atherogenic lipoproteins (e.g., TC, apoB, non-HDL-C and Lp(a)) were also statistically reduced from baseline vs. placebo.
- Trials were of fair to good quality with surrogate endpoints as the primary and secondary endpoint measures, along with safety as an outcome measure.
- Overall, the body of evidence is moderate in quality since the effect of mipomersen on health outcomes has not been established but its effect on

	<p>reducing cardiovascular events is biologically plausible based upon the very high risk for cardiovascular events in the HoFH population and mipomersen's effect on reducing LDL-C. Additionally, because of the scarcity of patients with HoFH, sample sizes are small.</p>
<b>Safety</b>	<ul style="list-style-type: none"> <li>• Injection site reactions (ISRs) and flu-like syndrome (FLS) occurred more commonly in the mipomersen groups vs. placebo and were a common reason for study withdrawal from the pooled phase III trials (ISR=5% and FLS=3%).</li> <li>• ALT increased <math>\geq 3</math>xULN (and AST to a lesser extent) in more than 12% of patients in all trials and up to 33% of patients in one trial versus none of the patients in the placebo group in 4/5 trials.</li> <li>• In pooled phase III clinical trials, 18% of mipomersen vs. 2% of those receiving placebo withdrew from therapy due to adverse events. <ul style="list-style-type: none"> <li>◦ Events that led to withdrawal: ISR (5%), ALT increase (3.4%), FLS (2.7%), AST increase (2.3%) and abnormal LFT (1.5%)</li> </ul> </li> <li>• <b>Boxed warning with regard to the risk for liver toxicity. There is a REMS associated with mipomersen with the goals of:</b> <ul style="list-style-type: none"> <li>◦ Educating providers of the risk of hepatotoxicity with mipomersen and reinforce the need to monitor patients as instructed in the approved labeling.</li> <li>◦ Restricting access to patients who have a clinical or laboratory diagnosis consistent with HoFH.</li> </ul> </li> <li>• The FDA reviewer concluded that the safety database of mipomersen supports its use in patients with HoFH since these patients are at very, very high risk for cardiovascular disease/events. It does not support the use of mipomersen in patients that are at lower risk.</li> <li>• Thus, because of the unknown risk for less common but severe adverse events, all patients receiving mipomersen should be carefully monitored for adverse events and events should be reported to the FDA.</li> </ul>
<b>Other Considerations</b>	<ul style="list-style-type: none"> <li>• Before initiating treatment with mipomersen, liver transaminases (ALT and AST), alkaline phosphatase and total bilirubin should be measured.</li> <li>• Lipid levels should be monitored every 3 months in the first year of treatment. <ul style="list-style-type: none"> <li>◦ Maximal LDL reduction should be observed after 6 months of therapy.</li> <li>◦ If after 6 months the reduction in LDL is not considered sufficient, providers must determine whether continued therapy is justified in light of the potential risk for liver toxicity.</li> </ul> </li> <li>• LFTs, ALT and AST at a minimum, should be measured monthly within the first year and then every three months thereafter.</li> <li>• If LFTs persistently increase to <math>\geq 3</math>xULN, refer to the product labeling for recommendations on monitoring or altering therapy or see warnings and precautions on page 10 of this drug monograph.</li> </ul>
<b>Potential Impact</b>	<ul style="list-style-type: none"> <li>• Use of mipomersen should be limited to those patients with a clinical or laboratory diagnosis of homozygous familial hypercholesterolemia (HoFH) and who are receiving maximum treatment with statins and other lipid lowering drugs.</li> <li>• Providers must complete the REMS training required by the FDA in order to prescribe mipomersen.</li> <li>• Mipomersen should not be used in patients with severe hypercholesterolemia or those intolerant to statins who do not have HoFH.</li> <li>• Mipomersen should not be combined with LDL apheresis because of the lack of data. <i>There is an ongoing study to determine the safety and efficacy of combined treatment with mipomersen and LDL apheresis.</i></li> <li>• Since there are no published outcomes trials for either mipomersen or lomitapide, the positioning of these agents relative to one another in patients with HoFH is unclear. An unpublished analysis of pooled data from three trials of mipomersen demonstrated a significant reduction in major cardiac adverse events in patients receiving mipomersen for one year. Additionally, there are numerous drug-drug</li> </ul>

interactions to consider and dietary supplement requirements for lomitapide, but not for mipomersen.

## Background

### Purpose for review

- FDA approval (January 2013)
- Evidence of need?
- Does mipomersen offer advantages to currently available alternatives?
- What safety issues need to be considered?
- Does mipomersen have specific characteristics best managed by the non-formulary process, prior authorization, and criteria for use?

### Other therapeutic options

Formulary Alternatives	Other Considerations (For example efficacy, dosing regimen, safety concerns, storage limitations, etc.)
None	
Non-Formulary Alternative (if applicable)	Other Considerations (For example efficacy, dosing regimen, safety concerns, storage limitations, etc.)
Lomitapide (JUXTAPID®)	Oral daily dosing, similar concerns for hepatotoxicity, gastrointestinal ADEs and potential for drug-drug interactions

## Efficacy (FDA Approved Indications)

### Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to March 2015) using the search terms <mipomersen> and <Kynamro>. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials, medical reviews and transcripts of FDA advisory committee meetings on the FDA website were reviewed for relevant information and the clinicaltrials.gov site was searched for planned, ongoing and completed trials. All randomized controlled trials published in peer-reviewed journals were included.

### Review of Efficacy

There is a single published clinical trial evaluating the safety and efficacy of mipomersen in reducing LDL and other atherogenic lipoproteins from baseline in patients with homozygous familial hypercholesterolemia (HoFH).<sup>2</sup> The mean age of randomized patients was 33 years, mean baseline LDL was 440 mg/dL (11.4 mmol/L) in the mipomersen group and greater than 80% of patients had genetic confirmation of HoFH. The primary outcome was the percent reduction from baseline in LDL-C. In addition, there is a two-year extension study that included 38 patients with HoFH.<sup>3</sup> In these studies, LDL-C was reduced from baseline a mean of 24-28%, apoB 27-31%, TC and apoB 21-28%, Lp(a) 17-31% and triglycerides by 3-17%.<sup>3</sup> In the trial by Raal of 45 patients with HoFH,<sup>2</sup> LDL reduction from baseline ranged from +2 to 82% on mipomersen, demonstrating a highly variable response in individual patients. There are no trials demonstrating an effect on cardiovascular outcome between mipomersen and placebo. Because of the extremely low prevalence of HoFH, an outcomes trial is not feasible. Patients were excluded from the trial if they had experienced a significant cardiovascular event within the preceding 12 months, had unstable angina, heart failure, uncontrolled hypothyroidism, history of significant renal or hepatic impairment, etc. Patients receiving LDL apheresis were also excluded from trials because the effect of apheresis on the pharmacokinetics of mipomersen is unknown. There is a trial underway to determine the added effect of mipomersen on LDL in patients receiving regular LDL apheresis and whether the interval between LDL apheresis treatments can be prolonged or apheresis discontinued altogether.<sup>4</sup> In general, a dose of 200 mg was given subcutaneously every week unless patients were <50 kg then 160 mg was administered.

An unpublished analysis of three trials involving mipomersen in patients with HoFH, HeFH or severe hypercholesterolemia demonstrated that treatment with mipomersen for one year resulted in a significant reduction in major cardiac adverse events (MACE). In the analysis and prior to treatment with mipomersen, 63% of patients experienced 146 events including myocardial infarction (MI) (n=39), revascularization (n=99), unstable angina (n=5) and stroke (n=3). Within two years after starting mipomersen, the rate of MACE dropped to 9% of patients having twelve events including MI (n=2), revascularization (n=6) and unstable angina (n=4). This represents a reduction in MACE from 61% in those not treated with mipomersen to 8.7% in those treated for one year.<sup>14</sup>

### HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Clinical Trial	Population	Primary Outcome	Results	Adverse Events/Comments																								
<b>Raal, et al.<sup>2</sup></b> R, DB, MC, PC  26 wk Tx 24 wk F/U Phase III  Mipomersen 200 mg subQ once/wk  N=45 completed	<b>HoFH</b> (12 years or older), mean age 33 yrs.  Mipomersen 200 mg subQ once/wk vs. placebo  LDL >130 mg/dL (3.4 mmol/L) on existing max-dose lipid lowering drugs.  <i>No LDL apheresis</i>	LDL-C from baseline vs. placebo at 26 weeks	51 enrolled (34 Mipo vs. 17 P), 45 completed trial (28 Mipo vs. 17 P) <b>Mean percent reduction from baseline*</b> <table><tr><th>Lipid</th><th>Mipo</th><th>P</th></tr><tr><td>LDL</td><td>24.7</td><td>3.3</td></tr><tr><td>apoB</td><td>26.8</td><td>2.5</td></tr><tr><td>TC</td><td>21.2</td><td>2.0</td></tr><tr><td>NonHDL</td><td>24.5</td><td>2.9</td></tr><tr><td>HDL</td><td>+15.1</td><td>+3.9</td></tr><tr><td>Lp(a)</td><td>31.1</td><td>7.9</td></tr><tr><td>TGs</td><td>17.4</td><td>+0.4</td></tr></table> Wide variability in % LDL reductions, +2 to 82%. Response was independent of baseline LDL, age, race or gender. Max LDL lowering was observed by 17 wks.  Mean baseline LDL was 11.4 mmol/L (440 mg/dL), which was reduced to a mean of 8.4 mmol/L (325 mg/dL) with Mipomersen.	Lipid	Mipo	P	LDL	24.7	3.3	apoB	26.8	2.5	TC	21.2	2.0	NonHDL	24.5	2.9	HDL	+15.1	+3.9	Lp(a)	31.1	7.9	TGs	17.4	+0.4	D/C due to ADEs: ISR (n=2), rash (n=1), ALT increase (n=1), non-compliant (n=1) and withdrawn consent (n=1).  MRI done at baseline for hepatic fat and redone only if ALT ≥3xULN 4 pts with ALT ≥3xULN, 2/4 had no ↑ in hepatic fat; 1/4 had a persistent rise in ALT with hepatic fat at baseline of 9.6%; that ↑ to 24.8% on Tx and 1/4 had ↑ ALT at baseline.  ADEs reported at a higher frequency in Mipo vs. P ISR=76 vs. 24%, flu-like Sx=29 vs. 24%, nausea=18 vs. 6%, chest pain=12 vs. 0%
Lipid	Mipo	P																										
LDL	24.7	3.3																										
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<b>Santos, et al<sup>3</sup></b> OL extension trial from 3 RCTs  Up to 2 years (median 18.2 mo)  Mipomersen 200 mg subQ once/wk  N=141	<b>HoFH (n=38) and HeFH (n=103)</b>  Only pts completing a phase III RCT were enrolled.  All pts received Mipomersen 200 mg subQ once/wk  <i>No LDL apheresis</i>  <i>(No placebo control)</i>	Percent change from baseline in LDL, apoB, TC, non-HDL, TG, VLDL, HDL, apoA-1 and Lp(a)	<b>Efficacy results at 1 yr for 111 pts and 53 at 2 yrs.</b> Mean percent <u>reductions</u> in lipid parameters from baseline remained consistent through 104 wks: LDL: 27-28% apoB: 28-31% TC and non-HDL: consistent with changes in LDL and apoB Lp(a): 17-21% HDL: +3-10% TG: 3-14%  No separate reporting of lipid changes between pts with HoFH vs. HeFH.	77/141 (55%) D/C Tx, 61/141 (43%) due to ADEs and 16/141 (11%) for other reasons. FLS remained constant during the extension trial and was the primary reason for study D/C.  33/141 (23%) had serious ADEs, 4 were felt to be related: membranous glomerular nephritis, atrial fib, appendicitis and biliary colic.  LFTS: 18/141 (13%) had																								

				<p>persistent ↑ in ALT of <math>\geq 3 \times \text{ULN}</math>, occurring 6-12 mo after Tx started</p> <p>27/65 (42%) had no ↑ in liver fat by MRI while 16/65 (25%) had ↑ of <math>&gt;20\%</math>. Once pts D/C Mipo, liver fat regressed towards baseline.</p> <p>Dipstick protein in urine (<math>\geq 2+</math>) occurred in 9 (6.4%), felt to be sporadic and incidental</p>
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ALT=alanine aminotransferase, DB=double-blind, D/C=discontinued, FLS=flu-like syndrome, F/U=follow up, HDL=high density lipoprotein, ISR=injection-site reaction, LDL=low density lipoprotein, LFTs=liver function tests, Lp(a)=lipoprotein(a), MC=multicenter, non-HDL=non-high density lipoprotein, P=placebo, PC=placebo-controlled, R=randomized, RCTs=randomized controlled trials, Sx=symptoms, TC=total cholesterol, Tx=treatment, ULN=upper limit of normal

\*Significant reductions from baseline in all lipid parameters except apolipoprotein A1 (apoA-1)

- The FDA approval of mipomersen was based upon one phase III clinical trial conducted in patients with HoFH and three additional phase III trials conducted in patients at high risk for cardiovascular disease but without a diagnosis of HoFH (refer to the off-label section for a summary of trials in patients without a diagnosis of HoFH). A total of 390 patients were included in these trials and were randomized 2:1, mipomersen to placebo.
- The manufacturer of mipomersen funded all of the trials.
- Trials were of fair to good quality with surrogate endpoints as the primary and secondary endpoint measures, along with safety as an outcome measure. Overall, the body of evidence is moderate in quality since the effect of mipomersen on health outcomes has not been established but its effect on reducing cardiovascular events is biologically plausible based upon the very high risk for cardiovascular events in the HoFH population and mipomersen's effect on reducing LDL-C. Additionally, because of the scarcity of patients with HoFH, sample sizes are small.

### Potential Off-Label Use

*In this section, only those trials investigating the use of mipomersen in populations where off-label use may be potentially considered were included. Therefore, studies in which mipomersen was compared to placebo in patients with mild to moderate hypercholesterolemia were not included.*

### Review of Efficacy

There have been five randomized, double-blind, placebo controlled trials examining the mean or median percent reduction in LDL-C from baseline between mipomersen and placebo in patients at high risk for adverse cardiovascular events who have severe hypercholesterolemia with or without a diagnosis of HeFH or patients who are statin intolerant<sup>5-9</sup>. In four of the trials, patients were being treated at baseline with stable maximally tolerated doses of statin +/- other lipid lowering medications. The primary endpoint in each of the trials was the mean or median percent reduction in LDL-C from baseline. Treatment with mipomersen or placebo lasted up to 28 weeks. In most of the trials, patients were followed for an additional period of time (e.g., 26 weeks) for safety purposes after the active treatment phase was completed. Mean age was less than 60 years and baseline LDL-C ranged from 122-278 mg/dL. The mean percent LDL-C reduction from baseline in the mipomersen group ranged from 21 to nearly 37% in four trials<sup>5-8</sup> while the median percent reduction in LDL-C was 47.3% in patients who were statin intolerant.<sup>9</sup> All reductions were statistically greater than placebo. Significant reductions in other atherogenic lipoproteins were observed in the mipomersen vs. placebo groups (see table below for detailed results). Interestingly, LDL-C reductions from baseline were more dramatic in women vs. men and occurred in more than one trial.<sup>6-8</sup> A statistically significant effect of mipomersen on HDL-C or ApoA1 was generally not observed. Exclusion criteria were similar among the trials and included unstable angina, congestive heart failure, uncontrolled endocrine

disorders, hepatic or renal disease, etc. Aside from the phase II dose-ranging trial<sup>5</sup>, mipomersen was administered as 200 mg subcutaneously once a week.

### HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA, SEVERE HYPERCHOLESTEROLEMIA AND STATIN INTOLERANT PATIENTS

Clinical Trial	Population	Primary Outcome	Results	Adverse Events/Comments
<b>Akdim, et al.<sup>5</sup></b> R, DB, MC, PC, Phase II dose ranging trial  7 to 13 wk Tx  Mipomersen 50- 300 mg subQ once/ wk  N=44	<b>HeFH</b> on existing max dose lipid lowering Tx.  Mean age: 47-54 yrs  LDL >130 and TG <400 mg/dL Mipo 50, 100, 200 and 300 mg x 8 doses.  300 mg dose was given for 13 wks  <i>No LDL apheresis</i>	Mean percentage reduction from baseline to day 43 (wk 7) in LDL  Other endpoints were exploratory and included LDL from baseline after 13 wks of 300 mg Mipo.	39/44 (89%) completed the short- term study. Mean baseline LDL: 164-207 mg/dL  <b>Mean reductions: (7 wks)</b> LDL: 21% Mipo 200, 34% Mipo 300 apoB: 23% Mipo 200, 33% Mipo 300 TG and Lp(a) were reduced from baseline but not significantly. Mean reductions: (13 wks-300 mg): LDL: 37% apoB: 37% Lp(a): 29% Reductions in LDL and apoB remained 3 or more months after the last dose	5 pts on Mipo D/C from the study, 3 due to ADEs (ISR and FLS), 1 withdrew consent and 1 who met a “stopping rule” (urine dipstick protein: >1 g/24 hr) after six 300 mg doses. This pt entered the trial with impaired renal fxn and proteinuria.  ALT ↑ ≥3xULN in 3 pts on Mipo 300 mg. CT showed steatotic liver with hepatomegaly in 2 pts and without steatosis in 1 pts. Unclear significance since baseline liver CTs were not performed.
<b>Stein, et al.<sup>6</sup></b> R, DB, PC, MC Phase III trial  28 wks (26 wk Tx)  Mipomersen 200 mg subQ once/wk  N=124	<b>HeFH</b> on existing max tolerated statin doses +/- other lipid lowering drugs for 12 wks  Mean age: 56 years  LDL >100 and TG <200 mg/dL  Mipomersen 200 mg subQ once/wk for 26 wks vs. P  <i>No LDL apheresis</i>	Mean percent change from baseline to 28 wks in LDL or 2 wks after stopping Tx in non-completers.	124 randomized (84 Mipo, 41 P). 114 completed (74 Mipo, 41 P)  Baseline LDL 143-153 mg/dL  <b>Mean reduction from baseline:</b> LDL 28% Mipo vs. +5.2% P 45% of pts achieved LDL <100 vs. 4.9% on P. Maximal effect on LDL observed at 21 wks. Reduction in LDL was independent of baseline LDL. Women had a more dramatic response than men (40.6% vs. 20% reduction)  <b>Selected secondary measures:</b> apoB: 26.3% Mipo vs. +7% P TC: 19.4% Mipo vs. +4% P Lp(a): 21.1% vs. no change P Non-HDL: 25% Mipo vs. +3.7% HDL: +2.5% Mipo vs. +5.8% P (NS)	9/84 (11%) Mipo D/C due to ADEs. Noncardiac chest pain (n=2), constipation (n=1), ISR (n=3, 1 also with FLS), ALT ≥3xULN with Sx (n=2), ALT ≥5xULN (n=1).  Serious ADEs occurred in 2 P (CAD and SVT) and 6 Mipo pts (basal cell cancer, angina, AMI, chest pain, PE and noncardiac chest pain). <i>All considered not to be  related to Tx.</i>  ISR were rated as more often moderate to severe in Mipo Tx pts. ISR and FLS were the most common reason for D/C in Mipo (7.2%) vs. none with P.



				<p>ALT <math>\uparrow</math> <math>\geq 3 \times</math>ULN occurred in 1 P (2.4%) vs. 12 Mipo pts (14.5%). 5 Mipo (6%) vs. 0 P pts had persistent <math>\uparrow</math> in ALT. 1 pt with ALT <math>\geq 10 \times</math>ULN</p> <p>MRI liver fat (done in 70% of pts). At 28 wks, liver fat was 6.2% Mipo vs. -0.5% P. Regression analysis correlated liver fat to increased ALT.</p>
<p><b>McGowan, et al.<sup>7</sup></b> R, DB, PC, MC Phase III Trial</p> <p>28 wks (26 wk Tx)</p> <p>N=58</p>	<p><b>HeFH (?)</b> with severe hypercholesterolemia on existing max tolerated lipid-lowering Tx.</p> <p>Mean age: 50 years</p> <p>LDL <math>\geq 300</math> mg/dL or LDL <math>\geq 200</math> mg/dL with known CAD</p> <p>Mipomersen 300 mg subQ once/wk for 26 wk. vs. P</p> <p><i>No LDL apheresis</i></p>	<p>Mean percent reduction in LDL from baseline to 2 wks after the end of treatment. For completers, that is at 28 wks.</p>	<p>58 pts randomized (39 Mipo, 18 P) 45 completed (25 Mipo and 16 P)</p> <p>16 patients (14 Mipo and 2 P) did not complete the study and were excluded from the per-protocol population for the following reasons: Inadequate time on study drug: Mipo: n=7, P=0 Large LDL difference between screening and baseline (stable LDL?): Mipo: n=4, P=2 Prescribed medication changes: Mipo: n=5, P=0</p> <p>Mean baseline LDL: Mipo: 278 mg/dL P: 251 mg/dL</p> <p><b>Mean percent change in lipoproteins: (all p&lt;0.001, unless specified)</b> LDL: 36% (95% CI -15.3 to -51.1%) Mipo vs. +12.5% P TC: 28.3% Mipo vs. +11.2% P apoB: 35.9% Mipo vs. +11.4% P Lp(a): 32.7% Mipo vs. 1.5% P Non-HDL: 33.9% Mipo vs. +142% P TG: 8.6% Mipo vs. +26.6% P (p=0.034) HDL: NS</p> <p>Women had greater response in reducing LDL than men: 44% vs. 27%, both significant vs. P</p> <p>26% of pts had a &gt;50% reduction in LDL (Mipo) vs. none on P</p> <p>End of trial, 67% of P pts vs. 28% of Mipo pts still met criteria for</p>	<p>9 pts D/C study due to ADEs (8 Mipo [21%], 1 P [5%]) Serious ADEs during Tx Mipo: 6, P: none Serious ADEs after Tx Mipo: 5, P: 1 Two were drug related (ALT, AST <math>\uparrow</math> and hepatic steatosis in 1 pt, CVA, angina with Prinzmetal angina in 1 pt).</p> <p>Following ADEs reported: ISR: Mipo 89.7%, 31.6% P FLS: Mipo 46.2%, 21.1% P ALT <math>\uparrow</math>: Mipo 20.5%, 0 P AST <math>\uparrow</math>: Mipo 12.8%, 0 P Hepatic steatosis: Mipo 12.8%, 0 P Cardiac events: Mipo 12.8%, 5.3% P</p> <p>ALT <math>\uparrow</math> <math>\geq 3 \times</math>ULN=31% vs. none P 8 Mipo D/C due to ADE: 6 due to ALT elevation, 2 of those met the stopping rules (&gt;8xULN and <math>\geq 3 \times</math>ULN with symptoms suggestive of liver involvement. 1 D/C due to ISR and 1 for FLS</p> <p>CT or MRI of liver and spleen at baseline which was repeated if ALT <math>\geq 3 \times</math>ULN on 2</p>

			LDL apheresis (those criteria not provided)	consecutive visits, 1 wk apart. 7/12 (58%) had increased liver fat and 3/7 (43%) had steatosis. Pts with increased liver fat had more dramatic lowering of LDL (77.4% vs. 44.1%)
<b>Thomas, et al.<sup>8</sup></b> R, DB, PC, MC Phase III Trial  26 wks Tx, 24 wk follow up for safety  N=157	<b>Pts with hyper-cholesterolemia and with or at high risk for CAD</b> on maximally tolerated lipid-lowering drugs  Mean age 59 years  LDL $\geq$ 100 mg/dL  <i>No LDL apheresis</i>	Mean percent reduction in LDL from baseline to 2 wks after last dose (wk 28)	N=105 Mipo and 52 P Mean LDL at baseline was approximately 122 mg/dL in each group.  <b>Mean reduction from baseline:</b> LDL: Mipo 36.9% vs. 4.5% (p<0.001) 76% of Mipo vs. 38% P achieved LDL <100 mg/dL 51% of Mipo vs. 8% P achieved LDL <70 mg/dL Maximal reductions were seen at 17 wks.  Women experienced a more dramatic reduction in LDL vs. men (41.2% vs. 32.7%, respectively) Both were statistically better than P in reducing LDL  Baseline LDL did not affect response.	Most common ADEs were ISR and FLS which occurred more in the Mipo vs. P groups and was the primary reason for study D/C in Mipo pts 54 pts withdrew from study (45 Mipo [43%] vs. 9 P [17%]) 28 D/C due to ADEs (26 Mipo and 2 P) D/C from Mipo for LFT elevation (n=7) and ISR (n=7). Others not specified. D/C from P (n=2) ADE not provided.  ALT $\uparrow$ in 10 Mipo pts vs. none in P  Average liver fat increased by a mean of 15.9% for Mipo vs. 0.6% P.  One death was reported in each group. 1 AMI with cardiogenic shock in P and 1 AMI and pneumonia dying from liver failure in Mipo (not felt to be causally related to Mipo)
<b>Visser, et al.<sup>9</sup></b> R, DB, PC  26 wks Tx, 26 wk follow-up  N=34	<b>Patients at high risk for CHD (some with HeFH) and statin intolerant.</b> (Intolerant to 2 statins: Myalgia 91%, LFT elevation 1.3%, neurologic Sx 9% and other 30%)  Mean age: 52-55	Median percent change from baseline to 2 wks after Tx stopped (28 wks)	1 patient randomized to Mipo was excluded prior to Tx. Mipo N=21, P=12  Baseline LDL: Mipo: 243 mg/dl P: 243 mg/dL  <b>Median percent reduction from baseline to 2 wks after last dose:</b> LDL: Mipo 47.3% vs. P 2%, p<0.001 TC: Mipo 36.9% vs. P 1.8%,	D/C due to ADEs: Mipo N=4 (19%, flu-like Sx, malaise, myalgia and transaminase increase). One pt met the criteria for stopping due to high ALT $\geq$ 10xULN P N=2 (17%: AMI and diarrhea)  2 serious ADEs: Mipo: coronary artery stenosis, P: AMI



	<p>years</p> <p>LDL &gt;130 mg/dL and TGs &lt;200 mg/dL</p> <p>Mipo subQ 200 mg once per wk x 26 wks.</p> <p><i>No LDL apheresis</i></p>		<p>p&lt;0.001</p> <p>ApoB: Mipo 46.2% vs. P 4.3%, p&lt;0.001</p> <p>Lp(a): Mipo 27.1% vs. P 0, p&lt;0.01</p> <p>TG: Mipo 28% vs. P +5.8%, p&lt;0.01</p> <p>HDL, ApoA (NS)</p> <p>Range in LDL reductions: 19-77% in the Mipo group</p>	<p>Most common ADEs: ISR (Mipo 95%, P 83%)</p> <p>↑ALT &gt;ULN in Mipo 81% vs. P 25%</p> <p>Persistent ↑3xULN were seen in 7 Mipo (33%) vs. none placebo.</p> <p>Hepatic MRS (done only if persistent ↑ ALT 3xULN) to assess for liver fat. Performed twice in 14/21 (67%) in Mipo vs. 1/21 (5%) P.</p> <p>Median hepatic fat in the Mipo group was 24.4%, range 0.8-47.3%. Hepatic steatosis (IHTG content &gt;5.6%) found in 12/14 (86%) of Mipo vs. 1/1 P</p> <p>4 pts had &gt;20% IHTG content and persistent ALT↑ ≥2xULN and were referred to hepatologist, 2 had liver biopsies. Both showed severe macrovesicular steatosis, minor lobular inflammation, some ballooning cells but minimal to no fibrosis (fibrosis grade 0-1).</p> <p>Limitation of safety study, hepatic fat content was explored only after persistent ↑ in ALT.</p>
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ADEs=adverse drug events, ALT=alanine aminotransferase, AMI=acute myocardial infarction, CAD=coronary artery disease, CT=computed tomography, DB=double blind, FLS=flu-like symptoms, fxn=function, IHTG=intrahepatic triglyceride, ISR=injection site reactions, MC=multicenter, MRS=magnetic resonance spectroscopy, P=placebo, PC=placebo controlled, PE=pulmonary embolism, R=randomized, SVT=supraventricular tachycardia

## Safety

(for more detailed information refer to the product package insert)

### Boxed Warning

### WARNING: RISK OF HEPATOTOXICITY

**KYNAMRO can cause elevations in transaminases. In the KYNAMRO clinical trial in patients with HoFH, 4 (12%) of the 34 patients treated with KYNAMRO compared with 0% of the 17 patients treated with placebo had at least one elevation in alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR) or partial thromboplastin time (PTT) [see Warnings and Precautions (5.1)].**

KYNAMRO also increases hepatic fat, with or without concomitant increases in transaminases. In the trials in patients with heterozygous familial hypercholesterolemia (HeFH) and hyperlipidemia, the median absolute increase in hepatic fat was 10% after 26 weeks of treatment, from 0% at baseline, measured by magnetic resonance imaging (MRI). Hepatic steatosis is a risk factor for advanced liver disease; including steatohepatitis and cirrhosis [see *Warnings and Precautions* (5.1)].

Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT, AST regularly as recommended. During treatment, withhold the dose of KYNAMRO if the ALT or AST are  $\geq 3$  x ULN. Discontinue KYNAMRO for clinically significant liver toxicity [see *Dosage and Administration* (2.3) and *Warnings and Precautions* (5.1)].

Because of the risk of hepatotoxicity, KYNAMRO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYNAMRO REMS [see *Warnings and Precautions* (5.2)].

#### Contraindications

- Moderate or severe hepatic impairment (Child-Pugh B or C) or active liver disease, including unexplained persistent elevations of serum transaminases.
- Known sensitivity to product components.

#### Warnings/Precautions

- Risk of hepatotoxicity. Mipomersen can cause elevation in transaminases and hepatic steatosis. The connection between hepatic steatosis and elevated transaminases has not been established. There is concern that hepatic steatosis can lead to cirrhosis over a few years of treatment. The clinical trials conducted to date are insufficient to detect this safety concern because of their small sample size and relatively short duration.
  - Liver function tests (LFTs) including ALT, AST, total bilirubin and alkaline phosphatase should be measured prior to initiation of mipomersen.
  - LFTs (at least ALT and AST) should be done monthly within the first year and every three months thereafter.
  - Mipomersen should be stopped for persistent or clinically significant LFT elevation (see table below for recommendations).
  - If transaminase elevation occurs with symptoms of liver injury (e.g., nausea, vomiting, abdominal pain, fever, jaundice, lethargy or flu-like symptoms), an increase in bilirubin  $\geq 2$ xULN or active liver disease, mipomersen should be stopped and the cause identified.

ALT or AST	Treatment and Monitoring Recommendations
$\geq 3$ x and $< 5$ x ULN	<ul style="list-style-type: none"> <li>• Confirm elevation with repeat measurement in 1 week.</li> <li>• In confirmed, withhold dosing, obtain additional LFTs if not already measured (e.g., total bilirubin, alkaline phosphatase and international normalized ratio [INR]).</li> <li>• If resuming mipomersen after transaminases resolve to <math>&lt; 3</math>xULN, consider monitoring LFTs more often.</li> </ul>
$\geq 5$ x ULN	<ul style="list-style-type: none"> <li>• Withhold dosing, obtain additional LFTs if not already measured (e.g., total bilirubin, alkaline phosphatase and international normalized ratio [INR]) and investigate to identify the probable cause</li> <li>• If resuming mipomersen after transaminases resolve to <math>&lt; 3</math>xULN, consider monitoring LFTs more often.</li> </ul>

*Recommendations based upon an ULN of approximately 30-40 international units/L.*

- Since alcohol may increase hepatic fat or worsen liver injury, patients should limit their consumption of alcohol to no more than one drink per day.

- Caution should be used when mipomersen is combined with other drugs that may cause liver injury (e.g., isotretinoin, amiodarone, and excessive doses of acetaminophen, methotrexate, tetracyclines and tamoxifen) since the effect of concomitant use with mipomersen is unknown. More frequently monitoring of LFTs may be indicated.
- The effect of combining mipomersen with other lipid-lowering drugs known to increase hepatic fat is unknown and therefore these combinations are not advised.
- Injection site reactions (ISRs) have been reported in 84% of patients and generally consist of one or more of the following: erythema, pain, tenderness, pruritis and local swelling.
- Flu-like symptoms, generally occurring within two days after a subcutaneous injection, may occur in 30% of patients and include one or more of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia malaise or fatigue.

### Safety Considerations (Clinical Trials)

- In the clinical trial of HoFH:<sup>2</sup>
  - 4/34 (12%) patients withdrew from mipomersen due to adverse events.
  - ALT increased  $\geq 3 \times \text{ULN}$  in 12% of patients (n=4)
  - MRI for hepatic fat done in pts with persistent increase in ALT ( $\geq 3 \times \text{ULN}$ ): 2/4 pts with no increase, 1/4 pts with an increase from baseline 9.6% to 24.8%, 1/4 pts had increased ALT at baseline.
  - Injection site reactions and flu-like syndrome was reported at a higher frequency in the mipomersen vs. placebo group.
- In the two-year extension trial, which included patients with or without HoFH:<sup>3</sup>
  - 61/141 (43%) withdrew due to adverse events. 66% experienced flu-like syndrome (FLS), 25% withdrew as a result, 9% had severe FLS.
  - 111 patients received mipomersen for 1 year and 53 for 2 years.
  - ALT increased  $\geq 3 \times \text{ULN}$  in 18/141 (13%) patients.
  - 16/65 (25%) had an increase in hepatic fat  $>20\%$ , while 27/65 (42%) had no increase.
  - Serious adverse events were reported in 33/141 (33%), 4 were considered related to treatment (membranous glomerular nephritis, atrial fibrillation, appendicitis and biliary colic).
- In the trials involving patients with or without HeFH and with severe hypercholesterolemia or intolerance to statins:<sup>5-9</sup>
  - In the 5 trials, study withdrawal due to adverse events ranged from 11-25% in the mipomersen group vs. 0-17% in the placebo group and withdrawal rates were numerically higher in 4/5 studies in the mipomersen group.
  - ALT increased  $\geq 3 \times \text{ULN}$  in up to 33% of patients on mipomersen vs. none in the placebo group in 4/5 trials.
  - MRI for percentage of hepatic fat was performed in patients with persistent elevation in ALT or as part of the study protocol. Median hepatic fat was increased and hepatic steatosis was observed in the mipomersen group (hepatic fat 9.6%) vs. placebo (hepatic fat 0.02%) in trials that evaluated hepatic fat. Maximum increase in hepatic fat was 46% in the mipomersen vs. 28% in the placebo group. Investigators commented that patients with persistently elevated ALT often had greater increases in hepatic fat and steatosis vs. placebo and more dramatic reductions in LDL-C.
  - In one trial<sup>9</sup>, four patients with intrahepatic triglyceride content of  $>20\%$  and persistent ALT elevation were referred to a hepatologist. Liver biopsies were performed in 2/4 patients who were found to have severe macrovesicular steatosis, minor lobular inflammation, some ballooning cells and minimal to no fibrosis after 26 weeks of treatment.
- Related to the mechanism of action of mipomersen, there is an increased incidence of clinically significant LFT elevation and a greater percentage of hepatic fat and hepatic steatosis in patients receiving mipomersen. These changes cause significant concern since hepatic steatosis increases the risk for advanced liver disease (e.g., steatohepatitis and cirrhosis).
- Because of the risk of liver toxicity associated with mipomersen, the FDA has limited approval and restricted use to those patients with a clinical or laboratory diagnosis of HoFH because the balance of the risks and benefits of mipomersen in this high-risk population is favorable. The safety and effectiveness of mipomersen in

patients without HoFH is unknown and therefore use should be avoided in these patients.

- There is a Risk Evaluation Mitigation Strategy (REMS) associated with mipomersen to assure safe use and consists of the following goals:
  - To educate providers of the risk of hepatotoxicity with mipomersen and reinforce the need to monitor patients as instructed in the approved labeling.
  - To restrict access to patients who have a clinical or laboratory diagnosis consistent with HoFH.

## Adverse Reactions

### Common adverse reactions

- Injection site reactions (ISRs) are reported in up to 84% of patients using mipomersen and 33% placebo and may consist of erythema, pain, tenderness, pruritis and local tissue swelling. Discontinuation of mipomersen due to ISRs was reported in 5% of patients from pooled phase III clinical trials.
- Flu-like syndrome (FLS) was reported in 30% of patients receiving mipomersen and may include one or more of the following: influenza-like illness, pyrexia, chills, malaise, arthralgia, malaise or fatigue. FLS generally occurs within 2 days of the subcutaneous injection and does not occur with every dose. Withdrawal due to FLS was reported to be 3% in pooled phase III clinical trials.
- Transaminase elevation:
  - In pooled phase III trials, ALT increased to  $\geq 3$  and  $< 5$  x ULN in 12% mipomersen vs. 1% placebo. ALT increased to  $\geq 5$  x ULN in 3% mipomersen vs. 0% placebo.
  - Persistent increases  $\geq 3$  x ULN occurred in 8% mipomersen vs. 0% placebo.
  - AST also increased, but to a lesser extent.
- Benign or malignant neoplasms occurred in 4% of mipomersen recipients vs. none on placebo.
- 9% mipomersen vs. 3% of placebo recipients had 1+ or more proteinuria by dipstick at the end of the trial.
- Other adverse events included angina or palpitations, headache, nausea, vomiting and abdominal pain, hepatic steatosis and hypertension (see product labeling for incidence vs. placebo).
- In phase III trials in patients with HoFH, platelets changed a median of  $-30.6 \times 10^3/\text{uL}$  in mipomersen vs.  $+8.1 \times 10^3/\text{uL}$  with placebo. In pooled phase III trials, platelets changed from baseline  $-23.8 \times 10^3/\text{uL}$  in mipomersen vs.  $-3.5 \times 10^3/\text{uL}$  with placebo.
- Although the significance has not been established, 38% of patients in the pooled phase III trials tested positive for antibody formation against mipomersen but efficacy response rates did not differ. In the extension trial, 72% tested positive for anti-mipomersen antibodies and there was a higher incidence of FLS in the antibody positive patients.

### Death/Serious adverse reactions

- There were four deaths in the mipomersen development program, 3 mipomersen (acute myocardial infarction (n=2) and acute myocardial infarction and pneumonia dying from liver failure) and 1 placebo (acute myocardial infarction with cardiogenic shock). None of the deaths were considered to be causally related to treatment.
- Serious events felt to be possibly related to mipomersen included: membranous glomerular nephritis, atrial fibrillation, appendicitis, biliary colic, ALT, AST and hepatic steatosis, cerebrovascular accident, angina and Prinzmetal angina

### Discontinuations due to adverse reactions

- In 18% of mipomersen vs. 2% of those receiving placebo withdrew from therapy due to adverse events from pooled phase III trials.
  - Events that led to withdrawal: ISR (5%), ALT increase (3.4%), FLS (2.7%), AST increase (2.3%) and abnormal LFT (1.5%)

**Post-marketing Experience**

- During post-approval use, idiopathic thrombocytopenic purpura was reported. However, because of the voluntary nature of adverse drug event reporting, it is not possible to estimate risk or establish a causal relationship between the drug and adverse event.

**Drug Interactions****Drug-Drug Interactions**

- No interactions were noted between mipomersen and simvastatin, ezetimibe or warfarin
- Caution should be used when mipomersen is combined with other drugs that may cause liver injury (e.g., isotretinoin, amiodarone, and excessive doses of acetaminophen, methotrexate, tetracyclines and tamoxifen) since the effect of concomitant use with mipomersen is unknown. More frequently monitoring of LFTs may be indicated.
- The effect of combining mipomersen with other lipid-lowering drugs known to increase hepatic fat is unknown and therefore these combinations are not advised.

**Drug-Food Interactions**

- Since alcohol may increase hepatic fat or worsen liver injury, patients should limit their consumption of alcohol to no more than one drink per day.

**Risk Evaluation***As of: April 20, 2015*

	Comments				
<b>Sentinel event advisories</b>	<ul style="list-style-type: none"> <li>None</li> <li>Sources: ISMP, FDA, TJC</li> </ul>				
<b>Look-alike/sound-alike error potentials</b>	<b>NME Drug Name</b>	<b>Lexi-Comp</b>	<b>First DataBank</b>	<b>ISMP</b>	<b>Clinical Judgment</b>
	Mipomersen 200 mg/mL prefilled syringe	None	None	None	Mifepristone Miltefosine Mupirocin Meropenem
	Kynamro®	None	None	None	Kazano Kanamycin
	<ul style="list-style-type: none"> <li>Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)</li> </ul>				

**Other Considerations****FDA Reviewer notes/information:**<sup>10</sup>

- In the mipomersen group, hepatic fat was  $\geq 5\%$  in 62% of patients vs. only 8% in placebo recipients. The FDA reviewer felt that data from pooled phase III trials, there was modest correlation with elevated ALT and increased hepatic fat.
- With regard to the increased incidence of cardiovascular events in the mipomersen vs. placebo group, the events were not adjudicated and the number of events was small preventing the FDA reviewer from drawing any conclusions regarding an increased risk.
- The incidence of benign and malignant neoplasms was higher in the mipomersen vs. placebo group. The FDA reviewer commented that the clinical development program was insufficient to assess and the differences were not clinically meaningful and therefore no conclusions can be drawn. Larger studies for longer periods of time are needed to further address cancer incidence.
- In the open-label extension trial of 141 patients, the mean length of the study was 19.8 months and median was 18.2 months. Nineteen percent (n=27) received treatment for 6-12 months, 16.3% (n=23) for 12-18 months, 14.2% (n=20) for 18-24 months, 12.1% (n=17) for 24-30 months and 7.8% (n=11) received treatment for >36 months.

- The FDA advisory committee voted 9 in favor and 6 against approval of mipomersen for reducing LDL-C in patients with HoFH. The reason for voting against was since the modest mean LDL-C lowering was not sufficient to balance the safety concerns, primarily liver toxicity.
- The FDA concluded that the potential for benefit outweighs the potential for liver toxicity but required a Risk Evaluation and Mitigation Strategy (REMS) for approval. (See safety considerations for goals of the REMS).
- Four post-marketing trials are required: 1) development and validation of a sensitive assay to assess for the presence of antibodies to double-stranded DNA to allow for testing of patients treated with mipomersen, 2) a trial to assess for the presence of antibodies that bind to double-stranded DNA among patients treated with mipomersen, 3) a long-term prospective observational study of patients with HoFH treated with mipomersen to evaluate the known and potential risks related to mipomersen, including liver toxicity, malignancy, and autoimmune disorders, and 4) an assessment and analysis of spontaneous reports of serious hepatic abnormalities, malignancy, and immune-mediated reactions in patients treated with mipomersen.
- The FDA reviewer concluded that the safety database of mipomersen supports its use in patients with HoFH since these patients are at very, very high risk for cardiovascular disease/events. It does not support the use of mipomersen in patients that are at lower risk.
- The reviewer concludes that if post-marketing surveillance in patients with HoFH and investigational use in patients that are of more moderate risk (e.g., severe HeFH) demonstrates that mipomersen is well tolerated, consideration should be given to requiring a large cardiovascular outcomes trial to document that mipomersen does reduce the risk for cardiovascular events in these populations.

## Dosing and Administration

### Dosing:

- Mipomersen 200 mg given subcutaneously once a week on the same day. If a dose is missed, the missed dose should be given but separated by at least 3 days from the next weekly dose.
- Mipomersen should not be given intramuscularly or intravenously.

### Administration:

- Mipomersen syringes must be refrigerated and allowed to reach room temperature for at least 30 minutes prior to administering.
- Qualified healthcare personnel should supervise the first subcutaneous injection of mipomersen.
- Mipomersen should be injected into the abdomen, thigh or outer arm. It should not be injected into areas of skin with active disease or injury such as sunburns, skin rash or infection, active areas of psoriasis, etc. Administration into tattooed skin and scars should be avoided.

### Recommended Monitoring:

- Before initiating treatment with mipomersen, liver transaminases (ALT and AST), alkaline phosphatase and total bilirubin should be measured.
- Lipid levels should be monitored every 3 months in the first year of treatment. Maximal LDL reduction should be observed after 6 months of therapy. If after 6 months the reduction in LDL is not considered sufficient, providers must determine whether continued therapy is justified in light of the potential risk for liver toxicity.
- LFTs, ALT and AST at a minimum, should be measured monthly within the first year and then every three months thereafter.
- If LFTs persistently increase to  $\geq 3 \times \text{ULN}$ , refer to the product labeling for recommendations on monitoring or altering therapy or see warnings and precautions on page 10 of this drug monograph.

## Special Populations (Adults)

Specific dosing adjustments in special populations are included under Dosing and Administration.

### Comments

#### Elderly

- In trials of HoFH, mean age was 31 years and oldest patient was 53. Pooled phase III trials with small numbers of patients 65 years or > showed a higher incidence of hypertension and edema vs. placebo or younger patients on mipomersen. Hepatic steatosis was also reported more commonly in older patients 13.6% vs. 10.4% in younger patients.



<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>No data in pregnant women. Category B, use in pregnancy only if clearly indicated.</li> </ul>
<b>Lactation</b>	<ul style="list-style-type: none"> <li>No data in lactating women. Animal studies show poor oral bioavailability. A decision should be made whether to stop nursing or to stop mipomersen.</li> </ul>
<b>Renal Impairment</b>	<ul style="list-style-type: none"> <li>No data in patients with renal impairment or those receiving dialysis. Therefore, because of the lack of data and the higher incidence of 1+ dipstick proteinuria, mipomersen is not recommended in patients with severe renal impairment, clinically significant proteinuria or those on renal dialysis.</li> </ul>
<b>Hepatic Impairment</b>	<ul style="list-style-type: none"> <li>No data in patients with liver impairment. Mipomersen is contraindicated in patients with clinically significant liver dysfunction, including patients with persistent elevation of liver transaminases.</li> </ul>
<b>Pharmacogenetics/genomics</b>	<ul style="list-style-type: none"> <li>No data identified.</li> </ul>

### Place in Therapy ( this section may be edited prior to final approval of document and web posting)

- Homozygous familial hypercholesterolemia is a rare, inherited condition caused by mutations in the LDL receptor gene. It is estimated to occur in 1 in a million births. The LDL receptor defect/mutation results in very high levels of LDL cholesterol (LDL-C), development of severe cardiovascular disease at an early age and premature death.<sup>11-13</sup> Existing lipid-lowering drugs do not sufficiently reduce LDL in these patients and statins are less effective since statins act in part by upregulating LDL receptors. Many of these patients require weekly or biweekly LDL apheresis to maintain lower LDL levels.
- Mipomersen is approved as an adjunct to diet and other lipid-lowering drugs to reduce LDL-C, ApoB, total cholesterol and non-HDL-C in patients with HoFH. Lomitapide (Juxtapid®) is another recently approved agent used as an adjunct to low fat diet and other lipid-lowering drugs to improve lipids in patients with HoFH. Both agents have REMS to restrict their use to those patients with a clinical or laboratory diagnosis of HoFH. Because both drugs can increase hepatic fat and steatosis, significant concern exists for progression to steatohepatitis and cirrhosis with longer duration of use. Because of the concern for liver toxicity, use of mipomersen and lomitapide should be avoided in lower risk populations and/or those without HoFH.
- Since there are very few patients diagnosed with HoFH, a clinical trial demonstrating a reduction in cardiovascular morbidity or mortality is not feasible. Evidence from several small, good quality trials demonstrate a statistically significant reduction in LDL-C, non-HDL-C, apoB, TC and Lp(a) versus placebo in patients with HoFH<sup>2-3</sup> and patients with severe hypercholesterolemia or statin intolerance.<sup>5-9</sup>
- The safety database of mipomersen is very limited due to the small numbers of patients who were studied in the clinical trials leading to FDA approval. Thus, because of the unknown risk for less common but severe adverse events, all patients receiving mipomersen should be carefully monitored for adverse events and events should be reported to the FDA.
- The FDA reviewer concluded that the safety database of mipomersen supports its use in patients with HoFH since these patients are at very, very high risk for cardiovascular disease/events. It does not support the use of mipomersen in patients that are at lower risk.
- Since there are no published outcomes trials for either mipomersen or lomitapide, the positioning of these agents relative to one another in patients with HoFH is unclear. Additionally, there are numerous drug-drug interactions to consider and dietary supplementation requirements for lomitapide, but not for mipomersen.
- This drug requires a national prior authorization before mipomersen can be prescribed.

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## Appendix A: GRADEing the Evidence

### Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
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High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.